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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,801	09/10/2003	Susan Chubinskaya	PU3680US3	5240

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EXAMINER	
MITCHELL, GREGORY W	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,801	CHUBINSKAYA ET AL.	
	Examiner	Art Unit	
	Gregory W. Mitchell	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *8,15,16 and 18-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-14,17 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Election filed June 13, 2005. Claims 1-28 are pending. Claims 8, 15-16 and 18-27 are withdrawn from consideration as being drawn to a non-elected species. Claims 1-7, 9-14, 17 and 28 are examined herein.

Election/Restrictions

Applicant's election with traverse of a compound of formula V in the reply filed on June 13, 2005 is acknowledged. The traversal is not persuasive because no grounds are given.

The requirement is still deemed proper, for the reasons of record, and is therefore made **FINAL**.

Claims 8, 15-16 and 18-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 13, 2005.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-14 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of arthritis with specific

compounds, such as BDA452, does not reasonably provide enablement for the treatment of arthritic diseases with any agent that attenuates annexin function or any agent with the structure of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The recitation, "an agent that attenuates annexin function," is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). ***The Nature of the Invention***:

The rejected claim(s) is/are drawn to an invention which pertains to the treatment of arthritic diseases with *any* agent that attenuates annexin function.

(2). ***Breadth of the Claims***:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass a treatment comprising the administration of *any* agent that attenuates annexin function. The nature of the invention is complex in that it potentially encompasses any compound.

(3). ***Guidance of the Specification***:

The guidance given by the specification as to what types of "agents" would be useful in a method of the instant invention is limited. Applicant discloses BDA452 as an agent useful in the instant invention. The specification does not teach that the scope of the invention is limited to this compound, however.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

A definition by function, as we have previously indicated, does not suffice to define the genus ..." at 1406 (empahasis added).

In the instant case, "an agent that attenuates annexin function," recited in the instant claims is purely a functional distinction. Hence, these functional recitations read on any compounds that might have recited functions. However, the specification merely provides a limited number of examples of compounds for the various kinds of functional compounds possible.

Thus, Applicant's functional language at the points of novelty fail to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicant's, neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted." *General Electric Co. v. Wabash Appliance Corp.* 37 USPQ at 468 (US 1938).

(4). ***Working Examples***:

The invention is limited to a working example of the treatment of arthritis with BDA452.

(5). ***State of the Art***:

The state of the art with regard to the treatment of arthritis is developed. The state of the art with regard to the treatment of arthritis with an agent which attenuates any annexin function is underdeveloped. It is noted, for example, that Dubois et al.

(*Journal of Rheumatology*, 22(7), 1230-1234) and Rodriguez-Garcia et al. (*Ann. Rheum. Dis.*, 55, 895-900) both teach that annexin V antibodies have a detrimental role in arthritic conditions by interfering with annexin V function, such as collagen II binding, inhibiting of phospholipidase A_2 activity, etc. Accordingly, the attenuation of these types of functions of annexin V would not be expected to be beneficial for the treatment of arthritic conditions. It is further noted that the entire class of compounds represented by compounds of formula I would not be expected to be effective in the treatment of athritic conditions because Hofmann et al. (*Journal of Biological Chemistry*, 273(5), 2885-94) teaches that the mere substitution of a chlorine at the 7 position of a benzodiazepine is known to provide nearly *opposite* results as the non-substituted analog as it pertains to annexin function.

(6). ***Predictability of the Art***:

The invention is directed to the treatment of arthritis utilizing an agent that attenuates annexin function in general, wherein the structure of those compounds is limited only by the function of the compounds. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully describe the genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of*

California v. Eli Lilly and Co. Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compounds represented by an "an agent that attenuates annexin function," which may encompass countless compounds. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman*

clearly support that the instant claimed invention is highly unpredictable.

(7). ***The Quantity of Experimentation Necessary***:

The specification fails to provide sufficient support of the broad use of any copound represented by "an agent that attenuates annexin function." As a result, one of skill in the art would be forced to perform an exhaustive search for the embodiments of any drugs having the function recited in the instant claim suitable to practice the claimed invention. It is further noted that even within the genus of benzodiazepines claimed in formula I, one of ordinary skill in the art would need to determine which compounds had the desired annexin function effect since small variations in structure are known in the art to render opposite results. This is particularly true in view of the teachings of Dubois et al. and Rodriguez-Garcia et al. because the inhibition of certain annexin functions are known in the art to be detrimental to the treatment of arthritic conditions.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9-14, 17 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hofmann et al. (*Journal of Biological Chemistry*, 273(5), 2885-94) in view of Miao et al. (USPN 6093723).

Hofmann et al. teaches BDA452 as an inhibitor of the calcium influx activity of annexin V (a binder of callogen II) (p. 2891-2). Hofmann et al. does not teach the treatment of arthritis with the claimed compounds.

Miao et al. teaches that agents that inhibit calcium influx are useful in the treatment of autoimmune diseases, inflammatory diseases, rheumatoid arthritis, etc. (col. 1, lines 10-44; col. 12, lines 35-59).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat arthritic conditions with the compound as instantly claimed because (1) Hofmann et al. teaches the compound as a known inhibitor of calcium influx; and (2) Miao et al. teaches calcium influx inhibitors as known for the treatment of inflammatory disorders, rheumatoid arthritis, etc. One would have been motivated to utilize the benzodiazepines of Hofmann et al. because of an expectation of success in treating athritic conditions with an agent known to possess functional capabilities known in the art to be useful therefor.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory W Mitchell whose telephone number is 571-272-2907. The examiner can normally be reached on M-F, 8:30 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gwm

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER